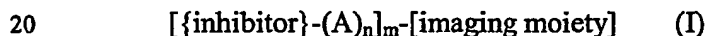


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ART 34 AMDT

CLAIMS.

1. An imaging agent which comprises a synthetic barbituric acid matrix metalloproteinase inhibitor labelled at the 5-position of the barbituric acid with an imaging moiety, wherein the imaging moiety can be detected following administration of said labelled synthetic barbituric acid matrix metalloproteinase inhibitor to the mammalian body *in vivo*, and said imaging moiety is chosen from:
 - (i) a radioactive metal ion;
 - (ii) a paramagnetic metal ion;
 - (iii) a gamma-emitting radioactive halogen;
 - (iv) a positron-emitting radioactive non-metal;
 - (v) a hyperpolarised NMR-active nucleus;
 - (vi) a reporter suitable for *in vivo* optical imaging;
 - (vii) a β -emitter suitable for intravascular detection.
2. The imaging agent of Claim 1, where the synthetic barbituric acid matrix metalloproteinase inhibitor ligand conjugate is of Formula I:



where:

{inhibitor} is the synthetic barbituric acid matrix metalloproteinase inhibitor;

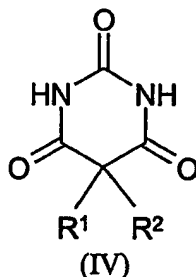
-(A)_n- is a linker group wherein each A is independently -CR₂-, -CR=CR-, -C≡C-, -CR₂CO₂-, -CO₂CR₂-, -NRCO-, -CONR-, -NR(C=O)NR-, -NR(C=S)NR-, -SO₂NR-, -NRSO₂-, -CR₂OCR₂-, -CR₂SCR₂-, -CR₂NR₂CR₂-, a C₄₋₈ cycloheteroalkylene group, a C₄₋₈ cycloalkylene group, a C₅₋₁₂ arylene group, or a C₃₋₁₂ heteroarylene group, an amino acid or a monodisperse polyethyleneglycol (PEG) building block;

R is independently chosen from H, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxyalkyl or C₁₋₄ hydroxyalkyl;

n is an integer of value 0 to 10; and

m is 1, 2 or 3.

3. The imaging agent of Claims 1 or 2, where the synthetic barbituric acid matrix
5 metalloproteinase inhibitor is conjugated to a ligand, and said ligand forms a metal complex with the radioactive metal ion or paramagnetic metal ion.
4. The imaging agent of Claim 3, where the ligand is a chelating agent.
- 10 5. The imaging agent of Claims 3 or 4, where the radioactive metal ion is a gamma emitter or a positron emitter.
6. The imaging agent of Claim 5, where the radioactive metal ion is ^{99m}Tc , ^{111}In , ^{64}Cu , ^{67}Cu , ^{67}Ga or ^{68}Ga .
- 15 7. The imaging agent of Claims 1 or 2, where the gamma-emitting radioactive halogen imaging moiety is ^{123}I .
8. The imaging agent of Claims 1 or 2, where the positron-emitting radioactive non-metal is chosen from ^{18}F , ^{11}C or ^{13}N .
- 20 9. The imaging agent of Claims 1 to 8, where the synthetic barbituric acid matrix metalloproteinase inhibitor is of Formula IV:



25 where:

R^1 is R'' or a Z group;

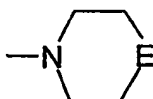
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PART 34 AMDT

R^2 is R'' , Y or $-NR^4R^5$, where R^4 is H or an R'' group, R^5 is H, C_{2-14} acyl, C_{2-10} aminoalkyl or (N- C_{2-14} acyl) C_{2-10} aminoalkyl or an R'' group, or R^4 and R^5 together with the N atom to which they are attached form an optionally (N- C_{2-14})acylated C_{2-8} cycloaminoalkylene ring;

R'' is independently C_{1-14} alkyl, C_{3-8} cycloalkyl, C_{2-14} alkenyl, C_{1-14} fluoroalkyl, C_{1-14} perfluoroalkyl, C_{6-14} aryl, C_{2-14} heteroaryl or C_{7-16} alkylaryl;

Z is a group of formula $-A^1O[A^2O]_pR^3$ where p is 0 or 1, and A^1 and A^2 are independently C_{1-10} alkylene, C_{3-8} cycloalkylene, C_{1-10} perfluoroalkylene, C_{6-10} arylene or C_{2-10} heteroarylene, and R^3 is an R group where R is independently chosen from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxyalkyl or C_{1-4} hydroxyalkyl;

Y is a group of formula:

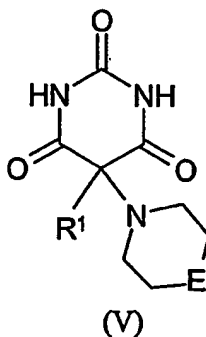


where E is CR_2 , O, S or NR^6 ; and R^6 is C_{2-14} acyl, or an R'' or Z group.

10. The imaging agent of claim 9, where R^2 is Y or $-NR^4R^5$.

11. The imaging agent of claims 9 or 10, where the imaging moiety is attached to the R^2 substituent.

12. The imaging agent of claims 9 to 11, of Formula V:



where E is CHR or NR^6 and R^1 is C_{6-14} *n*-alkyl, or C_{6-14} aryl.

13. The imaging agent of claim 12, where E is NR⁶ and R⁶ is C₂₋₁₄ acyl; -(CH₂)_dOH, where d is 2, 3, 4 or 5; or -C₆H₄X, where X is H, C₁₋₄ alkyl, Hal, OR, NR₂, NO₂ or SO₂NR⁷R⁸, where R⁷ and R⁸ are independently R groups, and R is as defined in Claim 9.
14. The imaging agent of claims 12 or 13, where R¹ is *n*-octyl, *n*-decyl, biphenyl, C₆H₅X or -C₆H₄-O-C₆H₄X where X is as defined in Claim 13.
15. A pharmaceutical composition which comprises the imaging agent of claims 1 to 14 together with a biocompatible carrier, in a form suitable for mammalian administration.
16. A radiopharmaceutical composition which comprises the imaging agent of claims 1 to 14 wherein the imaging moiety is radioactive, together with a biocompatible carrier, in a form suitable for mammalian administration.
17. The radiopharmaceutical composition of claim 16, where the imaging moiety comprises a radioactive metal ion.
18. The radiopharmaceutical composition of claim 16, where the imaging moiety comprises a positron-emitting radioactive non-metal or a gamma-emitting radioactive halogen.
19. A conjugate of a synthetic barbituric acid matrix metalloproteinase inhibitor with a ligand, wherein the barbituric acid comprises a 5-position substituent, and said 5-position substituent comprises a ligand capable of forming a metal complex with a radioactive or paramagnetic metal ion.
20. The conjugate of Claim 19, of Formula Ib:

[{inhibitor}-(A)_n]_m-[ligand] (Ib),

where {inhibitor}, A, n and m are as defined in Claim 2.

21. The conjugate of Claims 19 or 20, wherein the synthetic barbituric acid matrix
5 metalloproteinase inhibitor is of Formula IV or Formula V of Claims 9 to 14.
22. The conjugate of Claims 19 to 21, wherein the ligand is a chelating agent.
23. The conjugate of Claim 22, wherein the chelating agent has a diaminedioxime, N₂S₂,
10 or N₃S donor set.
24. A precursor for the preparation of the radiopharmaceutical composition of claim 18,
which comprises a non-radioactive derivative of the barbituric acid matrix
metalloproteinase inhibitor of claims 1 to 14, wherein said non-radioactive derivative
15 is capable of reaction with a source of the positron-emitting radioactive non-metal or
gamma-emitting radioactive halogen to give the desired radiopharmaceutical.
25. The precursor of Claim 24, where the source of the positron-emitting radioactive non-
metal or gamma-emitting radioactive halogen is chosen from:
- 20 (i) halide ion;
(ii) F⁺ or I⁺; or
(iii) an alkylating agent chosen from an alkyl or fluoroalkyl halide, tosylate,
triflate or mesylate;
(iv) HS(CH₂)₃¹⁸F.
- 25
26. The precursor of Claims 24 and 25, where the non-radioactive derivative is chosen
from:
- (i) an organometallic derivative such as a trialkylstannane or a trialkylsilane;
(ii) a derivative containing an alkyl or aryl iodide or bromide, alkyl tosylate or
30 alkyl mesylate for nucleophilic substitution;

- (iii) a derivative containing an aromatic ring activated towards nucleophilic or electrophilic substitution;
- (iv) a derivative containing a functional group which undergoes facile alkylation.
- 5 (v) a derivative which undergoes alkylation with an alkyl thiol to give a thioether.

27. A kit for the preparation of the radiopharmaceutical composition of Claim 17, which comprises the conjugate of Claims 19 to 23.

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28. The kit of Claim 27, where the radioactive metal ion is ^{99m}Tc , and the kit further comprises a biocompatible reductant.

29. A kit for the preparation of the radiopharmaceutical composition of Claim 18, which

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comprises the precursor of claims 24 to 26.

30. The kit of claim 29, where the precursor is bound to a solid phase.

31. Use of the imaging agent of Claims 1 to 14 for the diagnostic imaging of

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atherosclerosis.

32. Use of the imaging agent of Claims 1 to 14 for the diagnostic imaging of unstable plaques.

25 33. Use of the imaging agent of Claims 1 to 14 for the intravascular detection of atherosclerosis.